

**REMARKS**

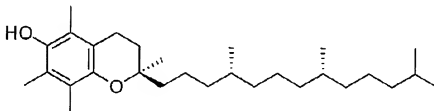
Claims 1-12 and 15-18 were previously pending in this application. Claims 19-24 have been added. Claims 4, 13, 14, and 17 are canceled. Claims 1-3, 5-12, 15, 16, and 18-21 are pending with claim 1, 20, 21, and 22 as the only independent claims.

**Rejections Under 35 U.S.C. § 112**

Claims 5-11 and 15-18 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner rejected claim 5 as unclear in view of phrases (e.g., in particular, such as, etc.) which are inappropriate to U.S. practice. Claim 5 has been amended to remove these phrases.

Applicants are not sure if the Examiner has objected to the use of the word "derivatives," but applicants assert that phrases such as derivatives of tocopherols and derivatives of tocotrienols would have meaning to a person of ordinary skill in the art. For example, vitamin E is a tocopherol and  $\alpha$ -tocopherol is a form of vitamin E with the structure set forth below.



A page from a German article is attached hereto as well as an English translation of pertinent portions thereof. That dictionary states that Vitamin E is a collective name for eight compounds: "the chemical compounds  $\alpha$ -tocopherol,  $\beta$ -tocopherol,  $\gamma$ -tocopherol and  $\delta$ -tocopherol and  $\alpha$ -tocotrienol,  $\beta$ -tocotrienol,  $\gamma$ -tocotrienol and  $\delta$ -tocotrienol." The same article states that "Tocopherol acetate, tocopherol succinate, tocopherol nicotinate and tocopherolpoly-(oxyethylene) succinate (International non-proprietaryname:Tocofersolate) are the usual dosage forms for the application of vitamin E." This would be the understanding of a person of ordinary skill in the art. See declaration. It is also consistent with a Wikipedia entry which describes vitamin E as a "collective name for a set of 8 related tocopherols and tocotrienols." In view of the foregoing and attached declaration, applicants submit there is nothing ambiguous about the description of derivatives in claim 5.

The Examiner rejected claim 6 as being unclear as to whether the coating is in the matrix or coating the matrix. The claim has been amended to say that the coating coats over the matrix.

Claims 8-10 have been amended to include Markush language.

Claim 15 has been amended to amend the typographical error "cop" to "cope."

#### **The Rejections Based Upon Art**

The Examiner rejected claims 1-5 and 15-17 as anticipated by Kiliaan et al. (WO 0184961), particularly noting example 1 in Kiliaan.

The Examiner rejected claims 1-5 and 15-17 as anticipated by Valle et al. (WO 92/11294).

The Examiner rejected claims 1 and 6-11 as obvious based upon USP 6,103,271 to Morrison et al. in view of USP 5,091, 187 to Haynes et al.

Claims 12 and 18 have not been rejected on art.

### **The References**

A. Kiliaan et al. Do Not Describe The Stable Solid Matrix And Shear Thinning Of The Claims.

The claims set forth ingredients in total and relative amounts which provide a solid at room temperature and also exhibit shear thinning or dilution. As noted at paragraph [0026] of the publication of Applicants' pending application:

Phosphatidyl serine and phosphatidyl choline are in particular stabilized according to the invention by other matrix components which are selected such that the total matrix (i.e. composed of PS/PC and the other components) is solid at room temperature and namely to such an extent that when using fats (triglycerides) the solid proportion of the triglyceride that can be determined by TLC is >80% at 23° C. In addition the components are advantageously selected such that the total matrix exhibits the property of shear dilution which for example can be achieved by the preferred use of a combination of fat and wax (e.g. bee wax) in conjunction with PC/PS in the matrix when the triglyceride contains a sufficiently high proportion of solid i.e. unmelted triglycerides.

Kiliaan et al. do not describe or suggest such a balancing of ingredients. Kiliaan et al. describe lower amounts of phosphatidyl serine than the claims because Kiliaan only describes active ingredients from which a percentage can be calculated. Kiliaan et al. describe preparations for the prevention and/or treatment of vascular disorders. Kiliaan's preparations require compounds which play a role in methionine metabolism in addition to having long-chain polyunsaturated fatty acids and phospholipids. In Kiliaan's Example 1, to which the Examiner refers (cf. page 13 of Kiliaan et al.), Kiliaan describes a capsule which contains folic acid and vitamin B12 in addition to phospholipids and eicosapentaenoic acid (EPA). The example, however, only lists the

active ingredients which are only part of the capsule and does not describe the whole capsule. The material of the capsule itself is not in the list of active ingredients of the Example. Consequently, the amounts indicated in Kiliaan's Example 1 only refer to the amounts of the active ingredient and cannot be directly compared to the amounts of claim 1 of the instant application. The claims herein refer to the total matrix. Because the weight of the active ingredients of Example 1 is about 830 mg, this means that phosphatidyl serine (120 mg) forms only 14.4 weight percent of the active ingredients and phosphatidyl choline (130 mg) forms only 15.6 weight percent of the active ingredients. This means that one can conclude that the coating of encapsulated composition itself exhibits a considerable additional weight. Thus, the amounts of phosphatidyl serine and fatty acids contained in Kiliaan's Example are lower than the amounts of claim 1 of the present application.

Kiliaan et al. do not describe a stable solid matrix. Because the amounts and relative amounts of phosphatidyl serine and fatty acids are lower than what is now claimed, the capsule described in Kiliaan's Example 1 is not a dosage form which becomes a solid matrix at room temperature, nor would it have the shear dilution as described in the claims. See attached declaration. Further, due to the amounts of fatty acids in Kiliaan's Example 1, there is no formation of a stable matrix. See attached declaration. Finally, the blend of Example 1 of Kiliaan et al. contains herbal extracts, which do not promote the stability of any matrix. See attached declaration. Hence, for these additional reasons, Kiliaan does not inherently disclose the claims.

Kiliaan et al. do not suggest any matrix which is solid or paste-like at room temperature and exhibits property of shear dilution, nor that the selection of the additional other components is of decisive importance in this respect in accordance with claim 1 of the invention.

The matrix of the invention, which is defined by the percentage amount of the specific components which confer to the whole matrix the characteristic features in accordance with the invention, namely that the total matrix is solid or paste-like at room temperature and exhibits property of shear dilution, is neither disclosed nor rendered obvious by Kiliaan et al.

B. Valle et al.

Valle et al. describe heparin formulations. Valle's Example 2.1 (page 36), to which the Examiner refers, describes a preparation for oral administration in pill or capsule dosage form. The active ingredient of the formulation is a heparin derivative (PE). Additionally, Valle's Example 2.1 describes phosphatidyl choline (PC), phosphatidyl serine (PS), as well as lactose and cellulose. Valle, however merely describes the total collective amounts (not relative amounts) of PS and PC. Valle does not describe individual amounts of PS and PC. Moreover, the two polyalcohol components, lactose and cellulose amount to 34.1% (w/w) altogether. In contrast, the polyalcohol component of claim 1 of this amendment amounts is less: 2-20 wt. %.

The compositions disclosed in Valle's Example 2.1 substantially differ from the matrix of claim 1 of the present amendment. Clearly Valle does not describe or suggest a balancing of ingredients as described in the claims of the instant application. The amounts of PS and PC are not disclosed and the amounts of the further components are not disclosed in the amounts set forth in the claims. Valle does not inherently anticipate the claims.

**The Claims Are Not Anticipated By Kiliaan or Valle**

Neither Kiliaan nor Valle describes all of the elements of the claims. Indeed, on their faces they are different from the claims. While there may be a way of carefully selecting one of the many thousands of ingredients disclosed by a reference to argue the claims are obvious, inherency and anticipation is not based upon possibilities or probabilities. *Roscco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380-81 (Fed. Cir. 2002); *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); and *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993); MPEP § 2112 (IV). The law does not permit the Examiner to assume there is an anticipation.

Kiliaan et al. or Valle et al., alone or in combination, do not disclose or render obvious the specific composition of the matrix in accordance with the invention nor their advantageous properties, such as excellent stability. Hence, the subject matter of pending claim 1, as well as the claims depending therefrom, are novel and inventive over Kiliaan and Valle.

**The Claims Are Non-Obvious Over Morrison et al. In View Of Haynes Because Neither Suggests The Claimed Matrix**

Claims 1 and 6-11 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,103,271 to Morrison et al. in view of U.S. Patent No. 5,091,187 to Haynes.

Morrison et al. discloses microcapsules that can be coated with several anionic coating compositions. Morrison et al states that these microcapsules are best created in a microgravity environment. Phosphatidyl serine and phosphatidyl choline are theoretically listed *inter alia* in column 18, Table VII of Morrison et al. However, the subject-matter of Morrison et al. differs from the present invention in that Morrison et

al. does not give any hint to the matrix of claim 1 of the invention having the specific percentage amount of the specific components which provide the whole matrix its characteristic features, namely that the total matrix is solid or paste-like at room temperature and exhibits property of shear dilution. Moreover, Morrison et al.'s microcapsules have alternating hydrophilic and hydrophilic liquid layers surrounded by flexible, semi-permeable hydrophobic or hydrophilic outer layers, whereas the pending claims require that the matrix is solid or paste-like at room temperature.

Further, starting out from Morrison et al., a person skilled in the art could not arrive at the subject-matter of claim 1 of the present invention by combining Morrison et al. with Haynes. Haynes describes water-insoluble drugs which are rendered injectable by formulation as aqueous suspensions of phospholipid-coated microcrystals. In particular, in column 13, line 65 of Haynes, phosphatidyl choline is mentioned as a useful membrane-forming lipid, and in column 14, line 11, phosphatidyl serine is mentioned as a phospholipid being capable of calcium-dependent aggregation. However, there is no hint in Haynes et al., to the matrix of the invention, which is defined by the specific percentage amounts of the components. Haynes et al. does not teach or suggest using specific quantities of specific combinations of constituents to form a matrix as claimed.

Applicants respectfully submit that the subject matter of newly specified claim 1 is inventive over Morrison et al. alone as well as in combination with Haynes.

#### Double Patenting

Claims 1-5 and 15-17 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 1-14 of copending U.S. Application Serial No. 10/511,884. Applicants bring to the Examiner's attention that

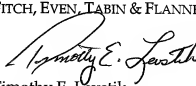
Application No. 10/511,888  
AMENDMENT  
Reply to Office Action of July 1, 2008

claims 1-14 of the '884 application were canceled in a Supplemental Preliminary Amendment filed May 4, 2005. Therefore, Applicants respectfully submit that the double patenting rejection is improper.

The Commissioner is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 06-1135.

Respectfully submitted,  
FITCH, EVEN, TABIN & FLANNERY

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## Attachment 1

Partial Translation

RÖMPP Online, Version 3.2

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### Vitamin E

Date: November 2004

Page 1, lines 1,2, and 4-7:

Collective name for the chemical compounds  $\alpha$ -tocopherol,  $\beta$ -tocopherol,  $\gamma$ -tocopherol,  $\delta$ -tocopherol and  $\alpha$ -tocotrienol,  $\beta$ -tocotrienol,  $\gamma$ -tocotrienol and  $\delta$ -tocotrienol.

Thereby, 1 mg  $\alpha$ -TE is 1 mg *RRR*- $\alpha$ -tocopherol or 2 mg *RRR*- $\beta$ -tocopherol or 4 mg *RRR*- $\gamma$ -tocopherol or 100 mg *RRR*- $\delta$ -tocopherol or 1,49 mg *all-rac*- $\alpha$ -tocopherol acetate. The International unit (IU) corresponds to 1 mg *all-rac*- $\alpha$ -tocopherol acetate.

Page 2, 3rd paragraph:

Tocopherol acetate, tocopherol succinate, tocopherol nicotinate and tocopherolpoly-(oxyethylene) succinate (International non-proprietary name: Tocofersolate) are the usual dosage forms for the application of vitamin E.

## Vitamin E

Stand: November 2004 > Bearbeitet von: Sandra Gredel  
Fachgebiet: Lebensmittelchemie > Unterthema: Vitamine  
Fachgebiet: Naturstoffe > Unterthema: Primärmetabolite, Fette, Oxylipine

Sammelbezeichnung für die chemischen Verbindungen  $\alpha$ -Tocopherol,  $\beta$ -Tocopherol,  $\gamma$ -Tocopherol,  $\delta$ -Tocopherol und  $\alpha$ -Tocotrienol,  $\beta$ -Tocotrienol und  $\delta$ -Tocotrienol. Nach Vorkommen und Wirksamkeit wichtigster Vertreter ist das  $\alpha$ -Tocopherol, weshalb Angaben zu Gehalt und Bedarf an Vitamin E meist als  $\alpha$ -Tocopherol-Äquivalente ( $\alpha$ -TE) gemacht werden. Dabei entspricht 1 mg  $\alpha$ -TE gleich 1 mg *RRR*- $\alpha$ -Tocopherol oder 2 mg *RRR*- $\beta$ -Tocopherol oder 4 mg *RRR*- $\gamma$ -Tocopherol oder 100 mg *RRR*- $\delta$ -Tocopherol oder 1,49 mg *all-rac*- $\alpha$ -Tocopherolacetat. 1 Internationale Einheit (IE) entspricht 1 mg *all-rac*- $\alpha$ -Tocopherolacetat.

Angaben zu Struktur, chemischen Eigenschaften, technologischem Einsatz, Synthese und Analytik finden sich unter dem Stichwort Tocopherole.

### Vorkommen:

Vitamin E ist nahezu ubiquitärer Bestandteil des unverseifbaren Anteils aller nativen Fette und Öle. Die weitaus reichsten Quellen sind Speiseöle, insbesondere Preßöle von Keimlingen und Samen (vgl. Tabelle 1).

Tabelle 1: Mittlere Vitamin-E-Gehalte ausgewählter Lebensmittel (mg/100 g eßbarer Anteil).

	$\alpha$ -Tocopherol	$\beta$ -Tocopherol	$\gamma$ -Tocopherol	andere	$\alpha$ -TE
pasteurisierte Trinkmilch	0,08	—	—	—	0,08
Frauenmilch	0,52	—	—	—	0,52
Hühnerei	0,70	—	0,35	—	0,74
Hering	1,50	—	—	—	1,50
Butter	2,20	—	—	—	2,20
Standardmargarine	14,00	—	—	—	14,00
Olivenöl	11,90	0,10	0,76	—	12,00
Maisöl	25,10	0,65	55,80	2,45	30,90
Weizenkeimöl	192,00	50,80	30,40	6,80	215,40
Haselnüsse	26,00	—	1,90	—	26,48
Spinat	1,60	—	0,12	0,78	1,60
Tomaten	0,80	—	0,13	—	0,80
Weizen, ganzes Korn	1,00	0,38	—	2,92	1,40

Vitamin E ist wenig hitzeempfindlich, dafür sehr lichtempfindlich und sauerstoffempfindlich. Zubereitungsverluste treten daher meist bei unsachgemäßer Lagerung und beim Erhitzen in Gegenwart von Luftsauerstoff auf.

### Funktion:

Vitamin E wirkt als lipophiles Antioxidans.  $\alpha$ -Tocopherol wird in biologische Membranen eingebaut; das Verhältnis zu Arachidonsäure beträgt 1:1000 bis 1:500. In Membranen schützt es Membranfettsäuren vor Lipidperoxidation, indem es als Radikalfänger fungiert. Tocopherol wird durch Ascorbinsäure und die Selen-haltige Glutathion-Peroxidase (EC 1.11.1.9) regeneriert. Darüber hinaus werden für Tocopherole eine Vielzahl von günstigen physiologischen Eigenschaften diskutiert, die bisher aber nicht zweifelsfrei nachgewiesen werden konnten, wie Reduzierung von Muskelschäden [1], Verzögerung diabetischer

Spätschäden [2], Verminderung des Risikos der Kataraktbildung [3], Verminderung des oxidativen Streß bei Rauchern [4], anticarcinogene Effekte (Langzeitaufnahmegergänzung mit  $\alpha$ -Tocopherol kann das Risiko der Entstehung bestimmter Krebsarten vermindern; siehe auch Krebsprophylaxe mit Vitaminen) [5,6], Reduzierung von Cytostatika-bedingten Spätschäden und des Arteriosklerose-Risikos [7], protektive Wirkung gegen Hautschäden [8] und Haarschäden [9], Wirkung als Nitritfänger und Inhibierung der *N*-Nitrosamin-Bildung *in vivo* [10]. Zur Wechselwirkung von Tocopherolen mit freien Radikalen, Phospholipase A und Membranen siehe Literatur [11-14].

Nicht oxidative Mechanismen einer Vitamin-E-Wirkung sind eine beobachtete Modulation der Signaltransduktion in der Zelle, ein Einfluß auf die Gentranskription und auf Entzündungsprozesse. Letzteres wird vor allem durch die Wechselwirkung mit dem Arachidonsäure-Stoffwechsel erklärt (Hemmung der Thromboxan-Synthese, Erhöhung der Prostaglandin-Synthese) [15].

Tocopherolacetat, Tocopherolsuccinat, Tocopherolnicotinat und Tocopherolpoly(oxyethylen)succinat (internationaler Freiname: Tocofersolat) sind die üblichen Applikationsformen für die Anwendung als Vitamin E.

### Ernährungsphysiologie:

**Resorption und Stoffwechsel:** Vitamin E wird im Dünndarm durch passive Diffusion resorbiert, in Chylomikronen (siehe Lipoproteine) eingebaut und auf dem Lymphweg zur Leber transportiert. Die Bioverfügbarkeit liegt bei durchschnittlich 30% und ist abhängig von der Art des gleichzeitig verzehrten Nahrungsfetts, der Vitaminosis und vom Enzymstatus im oberen Dünndarm. Pankreaslipasen und Gallensäuren sind unabdingbar für die Verfügbarkeit von Vitamin E. In der Leber erfolgt ein Einbau in das Plasmalipoprotein VLDL, wobei das dafür zuständige Enzym, das  $\alpha$ -Tocopherol-Transfer-Protein ( $\alpha$ -TTP), hoch affin zum  $\alpha$ -Tocopherol ist. Deshalb findet sich im Plasma vor allem  $\alpha$ -Tocopherol; die anderen Tocopherole und Tocotrienole werden zu einem großen Teil über die Galle ausgeschieden. Die Verteilung an die Gewebe ist eng an den Lipoprotein-Stoffwechsel gebunden. Normalerweise findet man bei Erwachsenen im Plasma 1,1 mg/dL (25  $\mu$ mol/L) Gesamt-Tocopherole bzw. 0,8 mg/dL (19  $\mu$ mol/L)  $\alpha$ -Tocopherol. Als Zeichen einer Unterversorgung gelten <0,7 mg/dL (16  $\mu$ mol/L) Gesamt-Tocopherol und <0,5 mg/dL (12  $\mu$ mol/L)  $\alpha$ -Tocopherol.

Der Hauptteil des Gesamtkörperbestands an Vitamin E ist im Fettgewebe und in der Muskulatur lokalisiert und unterliegt nur einem geringen Umsatz. Das  $\alpha$ -Tocopherol im Plasma wird täglich vollständig umgesetzt. Die scheinbare Halbwertszeit von bis zu 70 Stunden erklärt sich durch die kontinuierliche Resekretion aus der Leber.

**Katabolismus und Ausscheidung:**  $\alpha$ -Tocopherol-Radikale werden zum  $\alpha$ -Tocopherolchinon oxidiert und anschließend zum  $\alpha$ -Tocopherolhydrochinon reduziert. Weniger als 1% dieser Metabolite erscheinen im Urin, der Großteil des aufgenommenen  $\alpha$ -Tocopherols wird über die Faeces ausgeschieden. Nicht-oxidative Metabolite sind 2,5,7,8-Tetramethyl-2-(2'-carboxyethyl)-6-hydrochroman ( $\alpha$ -CEHC, siehe Abbildung), Verbindungen mit verkürzter Seitenkette aber intaktem Chroman-Ring.

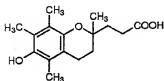


Abbildung:  $\alpha$ -CEHC.

Die in den 50er Jahren entdeckten Simon-Metabolite, Glucuronide und Sulfate von Tocopheronsäure und Tocopheronlacton, konnten nicht immer gefunden werden und scheinen Artefakte zu sein.

*Verzehrempfehlungen und Bedarf:* Der Bedarf an Vitamin E hängt, wie die folgende Übersicht zeigt, von der Zufuhr an ungesättigten Fettsäuren (mg  $\alpha$ -TE je g Fettsäure) ab:

- Monoen-Fettsäure: 0,06
- Dien-Fettsäure: 0,4
- Trien-Fettsäure: 0,6
- Tetraen-Fettsäure: 0,8
- Pentaen-Fettsäure: 1,0
- Hexaen-Fettsäure: 1,2

Zum Schutz der bei Stoffwechselvorgängen im Körper gebildeten Doppelbindungen vor Peroxidation gehen die D-A-CH-Empfehlungen (Referenzwerte für die Nährstoffzufuhr) neben diesem Fettsäure-abhängigen Bedarf von einem Grundbedarf von 4 mg  $\alpha$ -TE pro Tag aus. Die resultierenden Schätzwerte sind in Tabelle 2 dargestellt.

Tabelle 2: Schätzwerte für eine angemessene Zufuhr von Vitamin E.

Personengruppe	Alter	D-A-CH [mg $\alpha$ -TE/Tag] (männlich/weiblich)	RDA [mg $\alpha$ -TE/Tag]
Säuglinge	0–3 Monate	3	4
	4–11 Monate	4	5
Kinder	1–3 Jahre	6/5	6
	4–6 Jahre	8	7
	7–9 Jahre	10/9	7
	10–12 Jahre	13/11	11
	13–14 Jahre	14/12	11
	15–24 Jahre	15/12	15
Jugendliche und Erwachsene	25–50 Jahre	14/12	15
	51–64 Jahre	13/12	15
	>65 Jahre	12/11	15
Schwangere		13	15
Stillende		17	19

**Mangel:** Vitamin-E-Mangel ist beim gesunden Erwachsenen äußerst selten, tritt jedoch als Folge von Mutationen in den Genen für Apolipoproteine oder für das  $\alpha$ -TTP auf, was zu schweren neuromuskulären Störungen führen kann. Betroffen sind auch Patienten mit Zystischer Fibrose und Pankreasinsuffizienz. Häufig ist Vitamin-E-Mangel bei Frühgeborenen, bei denen stark erniedrigte Plasmatorocopherol-Werte, vermehrte oxidative Hämolyse, hämolytische Anämien, Ödeme und verstärkte Erregbarkeit beobachtet werden können.

Bei Ratten und Mäusen führt ausgeprägter Vitamin-E-Mangel zu Fertilitätsstörungen. Dieses Symptom konnte beim Menschen bisher nicht beobachtet werden.

### Toxikologie:

Verglichen mit Vitamin A oder Vitamin D ist Vitamin E bei oraler Aufnahme relativ untoxisch. Als obere, nebenwirkungsfreie Grenze der Zufuhr werden 200 mg  $\alpha$ -TE pro Tag angenommen, Tagesdosen bis 1000 mg gelten bei entsprechender Indikation als sicher. Allerdings können bei über 800 mg  $\alpha$ -TE/Tag die Thrombozytenaggregation gehemmt und die Blutungszeit verlängert sein. Verstärkte Vitamin-K-Mangelsymptome unter Antikoagulantien-Therapie mit Cumarin-Derivaten oder bevorstehende Operationen sind daher anerkannte Kontraindikationen für die Megavitamin-Therapie.

### Geschichte:

1920 zeigten Matill und Conklin, daß ausschließlich mit Milch gefütterte Ratten steril wurden, und Evans und Bishop stellten 1922 fest, daß Weizen-, Hafer-, Lattich- und Luzernenöle einen Faktor enthielten, der die Fertilitätsstörungen zu beheben vermochte. 1936 wurde dieser "Antisterilitätsfaktor" von Evans und Emerson aus dem Weizenkeimöl isoliert. Der Name Tocopherol ist von griechisch tokos = das Gebären und pherein = tragen, bringen abgeleitet. Fernholz gelang 1937 die Konstitutionsermittlung und P. Karrer und anderen kurz darauf (1938) die Synthese auf prinzipiell gleichem Wege wie heute. Natürliches RRR- $\alpha$ -Tocopherol ist ca. 1,7mal so wirksam wie das Syntheseprodukt all-rac- $\alpha$ -Tocopherol.

### Übersetzungen:

E vitamin E  
F vitamine E  
I vitamina E  
S vitamina E

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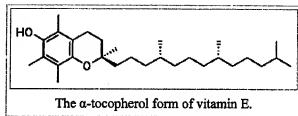
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## Attachment 3

# Vitamin E

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**Vitamin E** is the collective name for a set of 8 related tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties.<sup>[1][2]</sup> Of these,  $\alpha$ -tocopherol (also written as alpha-tocopherol) has been most studied as it has the highest bioavailability, with the body preferentially absorbing and using this form.<sup>[3]</sup>



It has been claimed that  $\alpha$ -tocopherol is the most important lipid-soluble antioxidant, and that it protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.<sup>[1][4]</sup> This would remove the free radical intermediates and prevent the oxidation reaction from continuing. The oxidised  $\alpha$ -tocopheroxyl radicals produced in this process may be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol or ubiquinol.<sup>[5]</sup>

The functions of the other forms of vitamin E are less well-studied, although  $\gamma$ -tocopherol (also written as gamma-tocopherol) is a nucleophile that may react with electrophilic mutagens,<sup>[3]</sup> and tocotrienols may have a specialized role in protecting neurons from damage.<sup>[6]</sup> However, the roles and importance of the various forms of vitamin E are presently unclear,<sup>[7][8]</sup> and it has even been suggested that the most important function of vitamin E is as a signaling molecule, and that it has no significant role in antioxidant metabolism.<sup>[9][10]</sup>

Most studies about **Vitamin E** have supplemented only alpha-tocopherol, but doing so leads to reduced serum gamma- and delta-tocopherol concentrations. For more info, read article tocopherol.

1 IU of vitamin E is the biological equivalent of about 0.667 mg d-alpha-tocopherol (2/3 mg exactly), or of 1 mg of dl-alpha-tocopherol acetate.

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## Food sources of Vitamin E

Particularly high levels of vitamin E can be found in the following foods:<sup>[11]</sup>

- Almonds
- Asparagus
- Avocado
- Nuts
- Olives

- Red Palm Oil
- Seeds
- Spinach and other green leafy vegetables
- Vegetable oils -- Canola, corn, sunflower, soybean, cottonseed
- Wheat germ

## Vitamin E and prostate cancer study discontinued

There have been some theories that Vitamin E, especially when coupled with selenium, may reduce the risk of prostate cancer<sup>[12]</sup> by 30 percent.<sup>[13]</sup> However, the Selenium and Vitamin E Cancer Prevention Trial, ("SELECT"), run from 2004 to 2008, found that vitamin E, whether taken alone or in combination with selenium, did not prevent prostate cancer.<sup>[14]</sup> The SELECT study was discontinued after independent reviewers determined that there was no benefit to the 35,000 men who were the subject of the study.<sup>[12]</sup>

## References

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## External links

- Vitamin E Medline Plus, Medical Encyclopedia, U.S. National Library of Medicine
- Vitamin E Office of Dietary Supplements, National Institutes of Health
- Jane Higdon, "Vitamin E", Micronutrient Information Center, *Linus Pauling Institute*

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